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Persistent neural activity during the maintenance of spatial position in working memory

Riju Srimal and Clayton E. Curtis*

Department of Psychology and Center for Neural Science, New York University, 6 Washington Place, New York, NY 10003, USA

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The mechanism for the short-term maintenance of information involves persistent neural activity during the retention interval, which forms a bridge between the cued memoranda and its later contingent response. Here, we used event-related functional magnetic resonance imaging to identify cortical areas with activity that persists throughout working memory delays with the goal of testing if such activity represents visuospatial attention or prospective saccade goals. We did so by comparing two spatial working memory tasks. During a memory-guided saccade (MGS) task, a location was maintained during a delay after which a saccade was generated to the remembered location. During a spatial item recognition (SIR) task identical to MGS until after the delay, a button press indicated whether a newly cued location matched the remembered location. Activity in frontal and parietal areas persisted above baseline and was greater in the hemisphere contralateral to the cued visual field. However, delay-period activity did not differ between the tasks. Notably, in the putative frontal eye field (FEF), delay period activity did not differ despite that the precise metrics of the memory-guided saccade were known during the MGS delay and saccades were never made in SIR. Persistent FEF activity may therefore represent a prioritized attentional map of space, rather than the metrics for saccades.

Keywords: Spatial; Working memory; Frontal eye field; Saccade; Attention

Introduction

Working memory allows animals to use information that is not currently available in the immediate environment. Without the ability to temporarily store information on-line, one's behavior is stereotyped and largely depends upon learned stimulus–response associations. If, however, an internal representation of critical information can be created and maintained for a short period of time, flexible behavior emerges because one's decisions can now utilize representations of temporally discontinuous events. Arguably, the most important scientific observation with regard to the neural mechanisms of working memory is that neuronal activity persists during the mnemonic delay period between a sensory cue (e.g., the position of a briefly flashed spot of light) and a later contingent motor response (e.g., a shift of gaze to the spot's remembered location) (Funahashi et al., 1989; Fuster and Alexander, 1971; Gnadt and Andersen, 1988; Kubota and Niki, 1971). It is thought that this activity reflects some form of a memory. Yet, it remains unknown what information is carried by the persistent activity, whether it represents, for instance, a retrospective code of the past stimulus or it represents a prospective code for the memory-guided response.

The frontal and parietal cortices are most strongly linked to working memory processes. Damage to or inactivation of these areas can cause severe working memory impairments (Curtis and D'Esposito, 2004; Dias and Segraves, 1999; Funahashi et al., 1993; Li et al., 1999; Lynch, 1992; Muri et al., 1996; Ploner et al., 1999; Rivaud et al., 1994b; Wardak et al., 2002). Additionally, parts of the frontal and parietal cortices show evidence of persistent neural activity during the retention interval of spatial working memory tasks in both monkeys using electrophysiology (Bruce and Goldberg, 1985; Chafee and Goldman-Rakic, 1998; Funahashi et al., 1989; Sommer and Wurtz, 2001; Umeno and Goldberg, 2001) and humans using functional magnetic resonance imaging (Brown et al., 2004; Courtney et al., 1998; Curtis and D'Esposito, 2006; Curtis et al., 2004; Geier et al., 2007; Leung et al., 2002; Medendorp et al., 2006; Postle et al., 2000; Postle and Hamidi, 2007; Rowe et al., 2000; Sala et al., 2003; Zarahn et al., 1999). These are critical pieces of evidence showing that parts of the frontal and parietal cortices are necessary for intact working memory and the mechanisms that underlie maintenance may be dependent upon persistent neural activity. Indeed, computational models of working memory hinge on the persistence of a signal throughout the retention interval until the memory-guided response can be generated (Machens et al., 2005; Wang, 2001).

Here, we used functional magnetic resonance imaging to identify the human cortical areas involved in maintenance and

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* Corresponding author.
E-mail address: clayton.curtis@nyu.edu (C.E. Curtis).
URLs: http://clayspace.psych.nyu.edu (R. Srimal), http://clayspace.psych.nyu.edu (C.E. Curtis).

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further tested hypotheses about what type of information is represented by persistent activity. With regard to our first goal – to identify areas whose activity persisted during memory delays – we used an event-related design that was optimized to evoke delay period activity that could be reliably measured. (1) We used memory delay periods that were variable in length and long in duration. The jittered delays helped statistically disambiguate blood oxygenation level dependent (BOLD) signals whose variance is best attributed to the delay period and not the bounding stimulus cue and motor response events. (2) It allowed us to unambiguously demonstrate that the activity persists until the response is made regardless of the delay length. (3) The variable delay helped keep subjects in an active state of maintenance since they could not predict when they were going to respond; with the use of fixed delay lengths, subjects learn that they do not need to remain in a state of readiness. Together, these features allow us to rigorously test for the presence of persistent delay period activity.

Our second goal was to test hypotheses about the nature of persistent activity, namely what type of information is carried by persistent activity. We asked if explicit foreknowledge about the metrics of the memory-guided response known throughout the retention interval influences persistent activity. We predicted that areas, like the human FEF, would show a greater magnitude of persistent activation when the precise metrics of the memory-guided saccade was known throughout the delay period. Our prediction was based on electrophysiological work in monkeys showing that pre-saccadic activity in FEF neurons is correlated with the metrics of saccades (Schall and Thompson, 1999). This hypothesis states that persistent activity is driven by neurons that code for the prospective saccade goal, a viable mechanism for performing memory-guided saccades.

To test that hypothesis, we compared delay period activity during a memory-guided saccade (MGS) task, the field's standard spatial working memory task, and during a spatial item recognition (SIR) task (Fig. 1a). During the MGS task, a single cued location was maintained during a delay after which a saccade was generated to the cue's remembered location. During the SIR task, which was identical to the MGS task until after the delay period, subjects never made an eye movement but instead made a button press that indicated whether a newly cued location exactly matched the remembered location. There were two key differences between the MGS and SIR tasks. First, subjects knew the precise metrics of the memory-guided response during the retention interval only in the MGS task; the button press response could not be predicted in the SIR task. This difference allowed us to test our prediction that cortical areas with saccade neurons (e.g., FEF) will show greater persistent activity during the delay period of the MGS compared to the SIR task. A second difference in the two tasks was that the motor effector used by the subjects to indicate their mnemonic response differed; saccades were used in the MGS task, while manual button presses were used in the SIR task. It was desirable to use a different response effector for a couple of reasons. Our main prediction, as described above, was that saccade neurons that code for the specific eye movement to the cue's location exhibit persistent activity during delay periods. If we used another task in which saccades were the response effector, a population of saccade neurons may increase in

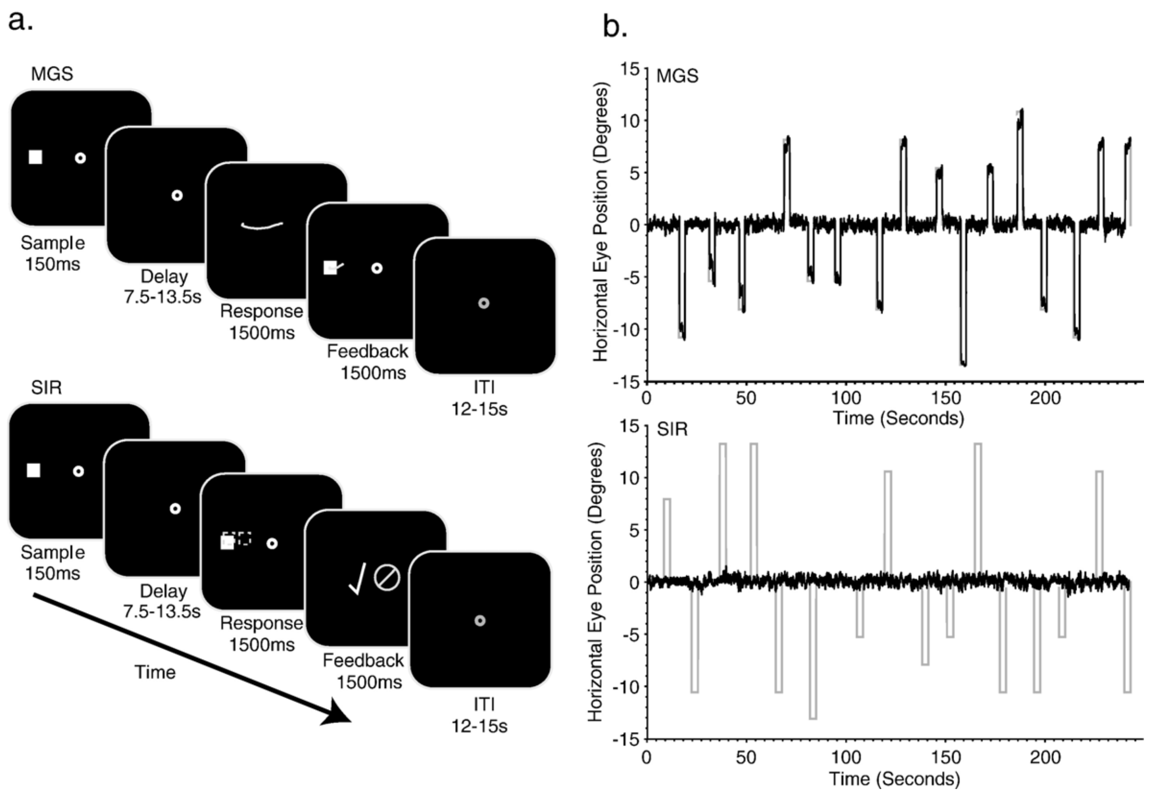

Fig. 1. (a) Schematic of the memory-guided saccade (MGS) and spatial item recognition (SIR) tasks. In both tasks, subjects maintained the position of a sample cue over a long and variable delay period. After the delay, subjects made a memory-guided saccade to the cued location in the MGS task. They decided whether a test cue matched the location of the sample cue (dotted box; was not visible to subject) in the SIR task. See Materials and methods for details. (b) Horizontal eye position traces from single blocks of the MGS and SIR tasks in an example subject (black line – eye position; grey line – target position).